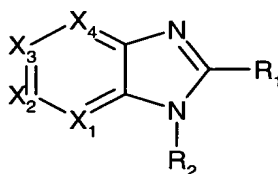


Amendments to the claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A compound of the general formula (I)



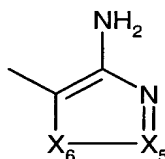
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X₁ is N or CR₃; X₂ is N or CR₄; X₃ is N or CR₅; X₄ is N or CR₆.

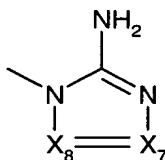
with the proviso that at least one but not more than two of X₁, X₂, X₃ and X₄ represents N.

R₁ is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d



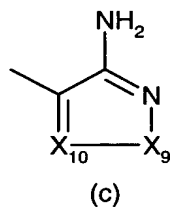
(a)

wherein X₅ is a group selected from N or CR₇ and X₆ is a group selected from O, S or NR₈;

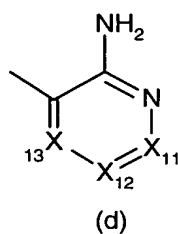


(b)

wherein X₇ and X₈ which may be the same or different is a group selected from N or CR₉;



wherein X_9 is a group selected from O, S or NR_8 and X_{10} is N or CR_{10} ;



wherein X_{11} , X_{12} and X_{13} may be the same or different and selected from a group N or CR_{11} ;

R_2 and R_8 independently represents hydrogen, hydroxy, aryl, heteroaryl, C_{3-7} -cycloalkyl, heterocyclyl, a group YR_{12} , $N=R_{13}$, $CONR_{14}R_{15}$,

$COCH_2NR_{19}R_{20}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$ or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} -cycloalkyl, heteroaryl, heterocyclyl, acylamino, NH_2 , $R_{19}NH$, $R_{19}R_{20}N$, $SO_2NR_{14}R_{15}$, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $OalkNR_{19}R_{20}$, $SalkNR_{19}R_{20}$ or $NR_{17}SO_2R_{18}$ group];

R_3 , R_4 , R_5 , R_6 , R_7 , R_9 , R_{10} and R_{11} independently represent a group selected from hydrogen, halogen, hydroxy, $R_{19}O$, $R_{19}S(O)_n$, NH_2 , $R_{19}NH$, $R_{19}R_{20}N$, nitro, formyl, C_{1-4} alkanoyl, alkenyl (optionally substituted by optionally substituted phenyl, heterocyclyl, or heteroaryl), carboxy, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$ or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} -cycloalkyl, heteroaryl,

heterocyclyl, NH_2 , R_{19}NH , $\text{R}_{19}\text{R}_{20}\text{N}$, acylamino, hydroxy, $\text{CONR}_{14}\text{R}_{16}$, $\text{NR}_{14}\text{COR}_{16}$, $\text{SO}_2\text{NR}_{14}\text{R}_{15}$, $\text{NR}_{17}\text{SO}_2\text{R}_{18}$, $\text{OalkNR}_{19}\text{R}_{20}$, or $\text{SalkNR}_{19}\text{R}_{20}$ group];

R_{19} and R_{20} independently represent a group selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

Y represents O, NH, NR_{12} or $\text{S}(\text{O})_n$;

R_{12} represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} cycloalkyl, heteroaryl, heterocyclyl, NH_2 , R_{19}NH , $\text{R}_{19}\text{R}_{20}\text{N}$, acylamino, hydroxy, $\text{CONR}_{14}\text{R}_{15}$, $\text{NR}_{14}\text{COR}_{16}$, $\text{SO}_2\text{NR}_{14}\text{R}_{15}$, $\text{NR}_{17}\text{SO}_2\text{R}_{18}$, $\text{OalkNR}_{19}\text{R}_{20}$, or $\text{SalkNR}_{19}\text{R}_{20}$ group]; R_{13} represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R_{13} represents a cycloalkylidene or heterocycloalkylidene group.

R_{14} and R_{15} independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} cycloalkyl, heteroaryl, heterocyclyl, NH_2 , R_{19}NH , $\text{R}_{19}\text{R}_{20}\text{N}$, or acylamino group] or R_{14} and R_{15} together with the nitrogen atom to which they are attached form a 4-7 heterocyclic ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O, N or $\text{S}(\text{O})_n$;

R_{16} and R_{18} independently represent, aryl, heteroaryl, heterocyclyl, cycloalkyl or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} cycloalkyl, heteroaryl, heterocyclyl, NH_2 , R_{19}NH , $\text{R}_{19}\text{R}_{20}\text{N}$, or acylamino group] or the group $\text{NR}_{14}\text{R}_{15}$ wherein R_{14} and R_{15} have the meanings defined above;

R_{17} represents hydrogen, aryl, heteroaryl, heterocyclyl, cycloalkyl or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7}

cycloalkyl, heteroaryl, heterocyclyl, NH₂, R₁₉NH, R₁₉R₂₀N, or acylamino group];

Alk is a C₂₋₄ straight or branched alkylene chain

n is zero, 1 or 2.

2. (Currently Amended) A compounds as claimed in claim 1 wherein only one of X₁, X₂, X₃ or X₄ represents N.
3. (Original) A compound as claimed in claim 2 wherein X₂ or X₃ represent N.
4. (Original) A compound as claimed in any of claims 1 to 3 wherein X₃ represents N.
5. (Original) A compound as claimed in claim 1 wherein X₁ and X₃ each represents N.
6. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 5] wherein R₁ is a group selected from (c) or (d).
7. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 6] wherein R₁ is a group (c) in which X₉ is oxygen and X₁₀ is nitrogen.
8. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 7] wherein R₂ represents hydrogen, C₁₋₆alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylmethyl, phenyl or phenyl substituted by(amino, dialkylamino, dialkylaminoalkylamino, alkyl, alkanoyl, alkoxy, halo, hydroxy, aminoalkyl, hydroxalkoxy, aminoalkoxy, alkylaminoalkoxy, N-aralkyl-Nalkylaminoalkoxy, aminocarbonylalkoxy, alkylaminocarbonylalkoxy, dialkylaminocarbonylalkoxy, ureidoalkoxy, alkylureido, dialkylamino-acetamido, alkylthioalkoxy, phenylthioalkoxy, alkylsulphinyalkoxy, phenylsulphinyalkoxy, alkylsulphonylalkoxy, phenylsulphonylalkoxy, cyanoalkoxy, acylaminoethoxy, alkylsulphonylaminoalkoxy phenylsulphonylaminoalkoxy, alkoxy carbonylalkoxy, heterocyclylalkoxy, heterocycliloxy, heterocyclyl), alkyl substituted by (hydroxy, amino, acylamino, R₁₉NH, R₁₉R₂₀N, a 4-7-membered heterocyclyl group), a 4-7

membered heterocyclyl group, a 5,6 fused bicyclic hetroaryl group, a 6,6 fused bicycliheterocyclic group, a 6,5 fused heterocyclic group or a 6,7 fused heterocyclic group.

9. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 8] wherein R₂ represents hydrogen, methyl, ethyl, isopropyl, sec butyl, 2-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclohexylmethyl, phenyl, phenyl substituted by[amino 4 - dimethylamino, dimethylaminoethylamino, N-methyl,dimethylaminoethylamino, N,N-bis(2-dimethylaminoethyl)amino), ethyl,acetyl, methoxy 3-methylbutoxy, chlorine, bromine,hydroxy, aminomethyl, 2-hydroxyethoxy, 3-hydroxypropoxy, 2- aminoethoxy, 2-methylaminoethoxy, 2-dimethylaminoethoxy, 2 diethylaminoethoxy, 2 diethylamino-1-methylethoxy, 2-disopropylamino-1-methylethoxy, N N-benzyl N-methylaminoethoxy, aminocarbonylmethoxy, aminocarbonyl-2-methylethoxy, aminocarbonylethoxy, methylaminocarbonylmethoxy, dimethylaminocarboxymethoxy, ureidomethoxy, 3-methylureido, dimethylaminoacetamido, methylthiomethoxy, phenylthiomethoxy, methylsulphinylmethoxy, phenylsulphinylmethoxy, methylsulphonylmethoxy, phenylsulphonylmethoxy, cyanomethoxy, 2-cyanoethoxy, t-butoxycarbonylaminoethoxy, isoxazolylaminoethoxy, isonicotinylaminoethoxy, methylsulphonylaminoethoxy, phenylsulphonylaminoethoxy, 2-methoxycarbonyl 1-methylethoxy, morpholinoethoxy, piperidinoethoxy, 1-pyrrolidino-2-ylmethoxy, 1-methyl-piperidino-4-yloxy or 3-pyrrolidinyl, 2-hydroxy-1-methyl-ethyl, 3- aminopropyl, 4-aminobutyl, 5 aminopentyl, 4-butyloxycarbonylamino-butyl, 2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl- butyl, 3-dimethylaminopropyl, 4-methylpiperazin-1-ethyl, 2-piperazin-yl-ethyl, piperidine 4-yl methyl, piperidine 3-yl methyl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 5-indazolyl or 6- indazolyl, .

tetrahydroisoquinolin-5-yl, 2-methyl tetrahydroisoquinolin-7-yl, 2-methanesulphonyl-tetrahydroisoquinolin-7-yl, tetrahydroisoquinolin-7-yl, 3,4 dihydro-2H-isoquinolin-1-one-7-yl, 2,3-dihydro-1H-isoindol-5-yl, benzo[1,3]dioxol-5-yl or 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl

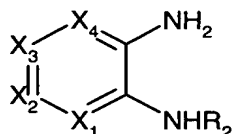
10. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 9] wherein R_3 represents hydrogen, halogen, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected from alkoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminoalkyl, alkyl, carboxyl carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy, $\text{CH}_3\text{S}(\text{O})_n$ wherein n is zero, 1 or 2, $\text{CH}_3\text{SO}_2\text{NH}$, or halogen), or heterocyclyl, heteroaryl, 6,5-fused bicycloheterocyclyl, an optionally substituted phenyl substituted by the group $\text{CH}_2\text{NR}_{19}\text{R}_{20}$ wherein R_{19} is alkyl, phenyl or a heterocyclic group and R_{20} is hydrogen or methyl, or $\text{NR}_{19}\text{R}_{20}$ is a 4-7 heterocyclic group, alkyl substituted by (a 4-7 membered heterocyclyl group or a group $\text{NR}_{19}\text{R}_{20}$ (wherein R_{19} is hydroxylalkyl, optionally substituted benzyl, C₃₋₇ cycloalkyl, a heterocyclic group, a 4-7 membered heterocyclalkyl or C₃₋₇ cycloalkylalkyl, R_{20} is hydrogen, methyl or acetyl), 4-heterocycloxy, heterocyclalkyloxy, vinyl (optionally substituted by optionally substituted phenyl), $\text{CONR}_{14}\text{R}_{15}$ wherein R_{15} is hydrogen, R_{14} is benzyl, phenethyl, aminoalkyl, 4-7 membered heterocyclyl or 4-7 membered heterocyclalkyl, or R_{14} and R_{15} together with the nitrogen atom to which they are attached represent a 4-7 membered heterocycl group, a group $\text{R}_{19}\text{S}(\text{O})_n$ (wherein n is zero, 1 or 2 and R_{19} is optionally substituted phenyl), or a group R_{19}NH and R_{19} is optionally substituted phenyl or heteroaryl.

11. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 10] wherein R_3 represents hydrogen, bromine, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected from methoxy, ethoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminomethyl, aminoethyl, methyl, ethyl, carboxyl, carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy, $\text{CH}_3\text{S}(\text{O})_n$ wherein n is zero, 1 or 2, $\text{CH}_3\text{SO}_2\text{NH}$, or fluorine), 5-methyl-1,2,4-oxadiazol-3-yl, 2-thienyl, 4-methylthienyl, 5-phenylthienyl, 5-formylthienyl, or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 3,5-dimethylisoxazol-4-yl, indolyl or 8-quinolyl, benzothienyl, 5-benzo[1,3]dioxolyl, a phenyl or fluorophenyl substituted by the group $\text{CH}_2\text{NR}_{19}\text{R}_{20}$ (wherein $\text{NR}_{19}\text{R}_{20}$ represents ethylamino, dimethylamino, 4-morpholino, pyrrolidino, piperidino, piperidin-4-yl-amino or 1-t butoxycarbonyl-piperidin-4-yl-amino.), 3-hydroxypropylamino, 4-bromobenzylamino, 4-methoxybenzylamino, 4-piperidinylaminomethyl, N-4-piperidinyl-N-methylaminomethyl, 1-t butoxycarbonyl-piperidinyl-aminomethyl, 4-aminopiperidinomethyl, 1,4-diazepan-1-ylmethyl, piperazinomethyl, 4-methylpiperazinomethyl, 4-acetylpiperizin-1-ylmethyl, 4-ethylpiperazinomethyl, 4-morpholinomethyl, piperidinomethyl, 4-(methylamino)piperidinomethyl, 4-cyclopropylaminopiperidinomethyl, pyrrolidinomethyl, 3-dimethylaminopyrrolidinomethyl, 2-hydroxymethylpyrrolidinomethyl, 4-ethylpiperazino-methyl, 3-pyrrolidin-1-yl-propylaminomethyl, 4-(4-fluorophenyl)piperazinomethyl, 3-piperidinyl-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-yl) propylaminomethyl, 1-methyl piperidin-4-yl-aminomethyl, 4-pyrrolidinocarbonylmethyl-piperazinomethyl, 2-pyrrolidin-1-ylmethylpyrrolidinomethyl, 2-pyrrolidin-1-yl-ethylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 1-methyl-piperidin-4-ylaminomethyl, 1-isopropyl-

piperidin-4-ylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 2-(morpholin-yl-methyl)-pyrrolidinomethyl, 3-piperidin-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-1-yl)propylaminomethyl, piperidin-1-ylmethylpyrrolidinomethyl, 3,5-dimethylpiperazinomethyl, pyrrolidin-1-ylpiperidinomethyl, pyrrolidino-3-ylaminomethyl, pyrrolidin-2-ylmethylaminomethyl, 4-aminomethylcyclohexylaminomethyl, 4-aminocyclohexylaminomethyl, 2-piperazin-1-ylethylaminomethyl, 3-amino-pyrrolidinomethyl, pyrrolidino-2-ylmethylaminomethyl, piperidin-4-ylmethylaminomethyl, 4-aminomethylpiperidinomethyl, 4-(cyclopropylaminopiperidinomethyl, 3-(piperazino-1-yl) propylaminomethyl, 2-(morpholin-4-ylmethyl)pyrrolidinomethyl, 2-(piperidin-1-ylmethyl)pyrrolidinomethyl, 2-(piperazin-1-ylmethyl)pyrrolidinomethyl, piperidin-4-ylmethyl, N-piperidin-4-yl-acetamidomethyl, piperidin-4-yloxy, or piperidin-4-ylmethoxy, 4-methyloxystyryl, $\text{CONR}_{14}\text{R}_{15}$

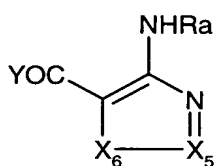
wherein R_{15} is hydrogen, R_{14} is benzyl, phenethyl, 3-aminopropyl, 4-aminobutyl, 6-aminohexyl, 3 or 4-piperidinyl, 1-aminomethylcarbonyl-piperidin-4-yl, 3-pyrrolidinyl, piperidin-2-ylmethyl or piperidin-4-ylmethyl, morpholin-2-ylmethyl or piperazinoethyl, or R_{14} and R_{15} together with the nitrogen atom to which they are attached represent piperazino, 1-methylpiperazino, 4-(2-aminoethyl)piperazino, 4-(t-butoxycarbonylaminoethyl)piperazino, 4-aminomethylcarbonylpiperazino, 4-aminoethylcarbonylpiperazino, 4-1-(aminoethylcarbonylpiperazino, 4-(1-methylaminoethylcarbonylpiperazino, 4-pyrrolidin-2-yl-carbonylpiperazino, pyrrolidino, 3-aminopyrrolidino, 2-methoxycarbonylpyrrolidino, morpholino, 2-(pyrrolidin-1-yl)methyl pyrrolidino, a group $\text{R}_{19}\text{S}(\text{O})_n$ wherein n is zero, and R_{19} is phenyl optionally substituted by methoxy, a group R_{19}NH wherein R_{19} is phenyl, 4-morpholinophenyl or 3-aminopyridyl.

12. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 11] wherein R₄ is hydrogen, methyl, methoxy, methylthio, phenylamino or phenoxy optionally substituted by fluorine or acetamido.
13. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 12] wherein R₅ is hydrogen, methyl, methoxy or phenoxy.
14. (Currently Amended) A compound as claimed in claim 1 [any of claims 1 to 13] wherein R₆ is hydrogen, chlorine, hydroxymethyl, methyl, methoxy, phenyl, 1-pyrrolidinyl or 1-pyrazolyl.
15. (Original) A pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt and or an N oxide thereof together with one or more pharmaceutically acceptable excipients and /or carriers.
16. (Original) A compound of formula (I) and/or physiologically acceptable salts thereof for use in therapy.
17. (Original) The use of a compound of formula (I) and/or a physiologically acceptable salt thereof in the manufacture of a medicament for inhibiting the effects of the kinase Msk-1 and or Rho-kinase 1 and or 2.
18. (Original) A method for inhibiting the effects of the kinase MSK-1 and or Rho-kinase 1 and or 2 comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.
19. (Original) A process for preparing a compound of formula (I) which comprises :-
- a) a process for preparing compounds of formula (I) wherein R₁ is a group (a), (c) and (d) by reacting the diamine (II)

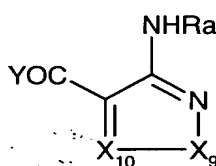


(II)

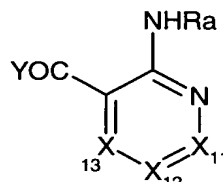
wherein R₂, X₁, X₂, X₃ and X₄ have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



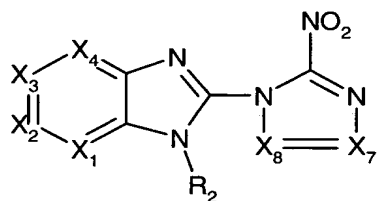
(IV)



(V)

wherein Y is hydrogen, halogen e.g. Cl, Br or I, hydroxy or C₁₋₄alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of X₅, X₆, X₉, X₁₀, X₁₁, X₁₂ and X₁₃ have the meanings as defined in formula (I) or is a group available thereto, followed when required by removal of the nitrogen protecting group Ra using conventional methods.

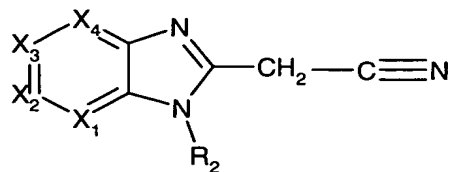
b) a process for preparing compounds of formula (I) wherein R₁ is the group (b) reducing of the corresponding nitro derivative (VI)



(VI)

wherein R₂, R₃, R₃, X₁, X₂, X₃, X₄, X₇ and X₈ have the meanings defined in formula (I).

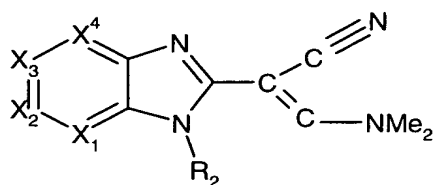
c) a process for the preparation compounds of formula (I) wherein R₁ is the group (c) and X₉ is oxygen and X₁₀ is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R_2 , X_1 , X_2 , X_3 and X_4 have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent and treatment of the product thus formed with a and hydroxylamine.

d) a process for preparing a compounds of formula (I) wherein R_1 represent the group (c) and wherein X_9 is NH and X_{10} is CH may be prepared by reacting compound (VIII)



(VIII)

wherein R_2 , X_1 , X_2 , X_3 and X_4 have the meanings defined in formula (I) with hydrazine.

and if necessary or desired:-

- i removal of any protecting groups
- ii converting one compound of the invention into another
- iii isolating the product of the reaction as a salt and or a solvate thereof